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## **Editorial**

### **Respiratory physiotherapy in the bronchiectasis guidelines. Is there a loud voice we are yet to hear?**

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A call for action for great awareness and research into airway clearance techniques and pulmonary rehabilitation in bronchiectasis.

Bronchiectasis is a chronic respiratory disease of airway dilatation, where patients typically suffer from respiratory infections, fatigue, sputum, cough, dyspnoea, and poor quality of life.(1, 2) This condition receives increased interest over the last years, with important developments in establishing national and international patient registries(3-5), randomized controlled trials of new treatments(6-8) and disease-specific health status questionnaires, such as the Bronchiectasis Health Questionnaire and the Quality of Life – Bronchiectasis.(9, 10) A number of new treatment approaches have been proposed including long term antibiotic therapies and immune modulating drugs.(6, 7, 11, 12)

Nevertheless the area of bronchiectasis care that has received the least attention during this period is the aspect of management that most healthcare professionals caring for bronchiectasis agree is the most important, airway clearance and exercise.(13, 14) The evidence base for respiratory physiotherapy has not advanced at the same pace as other aspects of bronchiectasis care.(15)

To assist clinical decision making, bronchiectasis guidelines synthesise, evaluate the evidence and provide recommendations for clinical practice, and a number of clinical guidelines in bronchiectasis have been published since 2008 (Table 1). Although usually similar, guidelines could present some variability in their recommendations even for the same topic.(16-21) This is particularly the case for physiotherapy because of the limited evidence on which to base guideline recommendations. The purpose of this editorial is to discuss the current state of play worldwide with regard to airway clearance and pulmonary rehabilitation and suggest the need to prioritise research into these topics.

Current guidelines for the clinical management of bronchiectasis are available from national and international organisations: the European Respiratory Society (ERS 2017), British Thoracic Society (BTS 2019), Thoracic Society of Australia and New Zealand (TSANZ 2015), Spanish Society of Pulmonology and Thoracic Surgery (SEPAR 2018), Brazilian Thoracic Association (BTA 2019) and Saudi Thoracic Society (STS 2017).(16-21) All guidelines refer to adults with bronchiectasis, whilst TSANZ and STS also include children.(16-21) Most documents are similar in that they are developed by multidisciplinary teams, used pre-defined PICO (patient, intervention, comparison, outcome) questions and used systematic literature searches to identify relevant evidence. To ensure integrity of the clinical guidelines, all members of the development panels disclosed conflict of interests, and in the ERS panel the conflicted members did not vote on recommendations that were of potential conflict. Moreover, some guidelines reported on the involvement of public or patient representatives.(16, 18, 21)

Bronchiectasis guidelines discuss airway clearance techniques, muco-active treatment and pulmonary rehabilitation to a variable extent, along with their corresponding evidence. The guidelines universally recommend that patients with bronchiectasis should be taught, and should practice individualised airway clearance techniques and that this is best delivered by a respiratory physiotherapist (Table 1). The grade of relevant recommendations ranges from weak (ERS, BTS) to strong (SEPAR, TSANZ) and the quality of relevant evidence is rated as low (SEPAR, ERS, BTS, STS) to moderate (BTS, TSANZ) (Table 1).(16-21) Overall, airway clearance

techniques show a short-term improvement in quality of life, cough-related measures and sputum volume expectoration compared to sham intervention and inactive control groups.(22, 23) A recent randomized controlled trial in 44 patients also demonstrated a reduction in exacerbations with twice daily airway clearance.(24) ERS, SEPAR, BTA and STS provide some examples of commonly practiced airway clearance techniques. BTS guideline recommends offering the active cycle of breathing techniques or oscillating positive expiratory pressure to patients, as well as considering gravity assisted positioning when this is not contraindicated.(18) Still, little is known about the benefits of a specific technique over others and data mainly come from small and short-term studies, often with a cross-over design.(22) BTS additionally presents a list of clinical practice advice for airway clearance techniques and suggests management flowcharts during a clinically stable state and an acute exacerbation. This guideline discusses issues such as adherence, frequency of airway clearance techniques and review sessions, under “good practice points”, derived from expert opinion.(18)

Mucoactive treatments (expectorants, mucolytics, mucokinetics, and mucoregulators) are also discussed in all bronchiectasis guidelines.(16-21) These suggest offering long-term ( $\geq 3$  months) muco-active treatment in patients with difficulty expectorating sputum when standard airway clearance techniques are not adequate to control symptoms, rather than routinely. Most guidelines provide a strong recommendation against the use of recombinant human deoxyribonuclease (rhDNase) in bronchiectasis, as this is associated with higher exacerbation rate, more hospitalisations and a greater FEV<sub>1</sub> decline.(25, 26) BTS provides a weak recommendation to use humidification with sterile water or normal saline.(18) TSANZ advocates to consider mucoactive treatment such as hypertonic saline and mannitol in patients with frequent exacerbations rather than routinely, as longitudinal randomised controlled trials found that these provided little benefit over isotonic saline and placebo treatment, respectively.(27, 28) There is therefore little clarity over when to use mucoactive treatments and how to define “difficulty expectorating sputum with standard airway clearance techniques”.

Regarding pulmonary rehabilitation, small (<85 participants) and mainly short-term but well conducted randomised controlled trials show clinically significant improvements in exercise tolerance and quality of life; incremental shuttle walk distance mean change (95% confidence intervals, CI) 67 (52, 82) m and St George’s Respiratory Questionnaire mean change (95% CI) -4.65 (-6.7, -2.6) units, respectively.(26) Nevertheless a systematic review shows the evidence base for pulmonary rehabilitation consists of only 4 trials and 164 participants.(29) A recent study showed that pulmonary rehabilitation is equally effective in COPD and bronchiectasis.(30) There is a unanimously strong (ERS, SEPAR, TSANZ, BTS) recommendation for participating in pulmonary rehabilitation programmes when patients present impaired exercise capacity or report exercise limitation due to breathlessness. This recommendation was supported by moderate (TSANZ, SEPAR, STS) to high (ERS, BTS) quality of evidence.(16-21) When defined, exercise limitation due to breathlessness is indicated by a Modified Medical Research Council (MMRC) Dyspnoea scale score of  $\geq 1$ , which refers to the person that gets short of breath when hurrying on level ground or walking up a slight hill or feels

breathless even easier than that. ERS, BTS and SEPAR consider the addition of inspiratory muscle training to support the maintenance of the exercise benefit, although there are no evidence of an additive benefit to exercise tolerance or other clinical outcomes.(17, 18, 31) Availability of pulmonary rehabilitation in many countries in Europe is limited due to lack of resources and the lack of evidence.

Guidelines support airway clearance and the use of mucoactive treatment based on low to moderate level of evidence, which indicates that further research could change our confidence in the estimated effect. On the other hand, pulmonary rehabilitation is supported by moderate to high quality of evidence, providing greater confidence on the effect of this treatment. Patients seem to accept and value airway clearance techniques and pulmonary rehabilitation but long term compliance with them is unknown.(32) Moreover, airway clearance and pulmonary rehabilitation bronchiectasis recommendations largely rely on studies during a clinically stable stage. Thus, clinically, we are mainly called to extrapolate these results to disease exacerbations or assume that clinical outcomes will resemble those of other respiratory conditions; this could be misleading.

The evidence base for bronchiectasis therapy is evolving, but whereas several thousand patients have now been enrolled into trials of high cost therapies such as inhaled antibiotics or inhaled mucoactive drugs, trials that have been largely unsuccessful, there have been no large trials of airway clearance and pulmonary rehabilitation.(6, 8, 33) A search of Clinicaltrials.gov and other trial databases identified no trials with >100 participants of these two interventions. The UK CLEAR trial of hypertonic saline and carbocysteine is an encouraging development that will recruit 380 patients (ISRCTN89040295). The absence of standardised, quality assured airway clearance across centres participating in pharmacotherapy trials has been cited as one potential reason for their heterogeneous results.(34, 35)

Preliminary data show that access to airway clearance techniques and pulmonary rehabilitation is highly variable in patients with bronchiectasis across Europe.(35, 36) Bronchiectasis audits have also shown that implementation of the guidelines can be limited and even adherence to national standards on patient care is variable.(37-40) In the era of evidence-based medicine, evidence for what is considered usual care and a core part of bronchiectasis management is paramount for the implementation of the best available treatment. Once high-quality studies, evidence and strong clinical guidelines are available, our aim could focus on the local implementation. Still, it seems a long way to that, and the question remains “how could we address these outstanding uncertainties as a community”?

We issue a call to action, urging researchers, clinicians, funding bodies and the European Respiratory Society to prioritise airway clearance and pulmonary rehabilitation. Large randomized studies of these interventions are feasible, particularly with the availability of large registries and recently developed standardised endpoints.(41)

Clinical guidelines since 2008 have underlined the need for high quality evidence to support these therapies that bronchiectasis patients are recommended on a daily basis. Questions

that remain unresolved include the role of airway clearance in stable disease and exacerbation, the optimum method of clearance, duration and frequency for improving long term and clinically important outcomes in various disease severities. We need more data about the impact of airway clearance and pulmonary rehabilitation treatments in numerous areas, particularly exacerbations and hospitalisations; the role of physiotherapists in individualised action plans and home intravenous antibiotics; education in pulmonary rehabilitation; self-management; treatment compliance; and links between primary and secondary healthcare.

Airway clearance is largely individualised, and this remains a profound research challenge. It is acknowledged that large clinical trials including a comparator arm of no physiotherapy present ethical and logistical challenges as airway clearance is a standard part of care, and blinding is challenging. Innovative trial designs including cluster randomized approaches, active comparator studies or step-wedge implementation trials are alternatives which can overcome any barriers.

Great steps forward have been taken in changing bronchiectasis from an “orphan disease” but respiratory physiotherapy remains an orphan topic even in this “age of bronchiectasis”. This has to change, for the benefit of all our patients.

**Conflict of interest**

**James D. Chalmers** has received research grants from Glaxosmithkline, Boehringer Ingelheim, Astrazeneca, Pfizer, Grifols, Bayer AG, Polyphor and Insmed; and received consultancy, congress travel or speaker fees from Glaxosmithkline, Bayer Healthcare, Aradigm Corporation, Grifols, Pfizer, Boehringer Ingelheim, Napp and Insmed.

**Arietta Spinou:** none.

*Table 1. Bronchiectasis clinical guidelines and their development methodology.*

Guideline developers	Year	Databases of review	Last date of search	Level of evidence appraisal system
<b>ERS</b>	<b>2017</b>	PubMed -MEDLINE-, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Library	Dec-16	GRADE
<b>BTS</b>	2010, <b>2019</b>	PubMed -MEDLINE-, EMBASE, Cochrane Library, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), NHS Economic Evaluation Database (NHS EED)	Jun-16	SIGN
<b>SEPAR</b>	2008, <b>2018</b>	PubMed -MEDLINE-, EMBASE, Cochrane Library, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA)	Feb-17	GRADE
<b>TSANZ*</b>	2008, 2010, <b>2015</b>	PubMed, Cochrane Central Library	Oct-13	Revised GRADE
<b>BTA**</b>	<b>2019</b>	NR	NR	NR
<b>STS*</b>	<b>2017</b>	Not reported	Not reported	Costume-made appraising (A, B, C, D)

Current guidelines are in bold.

\*: indicates that the guidelines include recommendations for children

\*\*This guideline used a narrative literature review.

NR: none reported.

Costume-made appraising system: A indicating high quality of evidence from RCTs and meta-analysis to D panel consensus

#### **Abbreviations:**

ERS: European Respiratory Society, BTS: British Thoracic Society, SEPAR: Spanish Thoracic Society, TSANZ: Thoracic Society of Australia and New Zealand, BTA: Brazilian Thoracic Association, STS: Saudi Thoracic Society, GRADE: Grading of Recommendations Assessment, Development and Evaluation, SIGN: Scottish Intercollegiate Guidelines Network grading system.

Table 2. Overview of respiratory physiotherapy recommendations in current clinical guidelines.

Guidelines	Recommendation	Grade of recommendation	Quality of evidence
<b>Airway clearance techniques</b>			
<b>ERS 2017</b>	<ul style="list-style-type: none"> <li>teach ACT by respiratory physiotherapist</li> <li>perform ACT once or twice daily in chronic productive cough or difficulty to expectorate</li> </ul>	weak	low
<b>BTS 2019</b>	<ul style="list-style-type: none"> <li>teach ACT to perform</li> <li>offer ACBT or o-PEP</li> <li>consider gravity assisted positioning where not contraindicated to enhance effectiveness of ACT</li> </ul>	D D	3 to 1- 1-
<b>SEPAR 2018</b>	<ul style="list-style-type: none"> <li>ACTs are safe</li> <li>in stable bronchiectasis with productive cough (hypersecretion or frequent exacerbations)</li> </ul>	strong	low
<b>TSANZ 2015</b>	<ul style="list-style-type: none"> <li>perform ACT</li> <li>get respiratory physiotherapist's advice</li> <li>individualise ACT</li> </ul>	strong	moderate
<b>BTA 2019</b>	<ul style="list-style-type: none"> <li>teach and apply ACT to all patients with chronic production of secretions and/or (CT scan) signs of mucus plugging</li> </ul>	NR	NR
<b>STS 2017</b>	<ul style="list-style-type: none"> <li>lack of data about role of ACT in acute exacerbation, it may be used if no contraindications</li> <li>consider patient's preference and adherence to treatment</li> <li>teach patient or caregiver and encourage use of ACT and appropriate device</li> <li>ACT is safe and may improve sputum expectoration, lung function and quality of life in stable bronchiectasis</li> </ul>	NR   NR	D   C
<b>Mucoactive treatment</b>			
<b>ERS 2017</b>	<ul style="list-style-type: none"> <li>long-term mucoactive treatment in difficulty to expectorate sputum and poor quality of life, and where ACT cannot control symptoms</li> <li>rhDNase is contraindicated</li> </ul>	weak  strong	low  moderate
<b>BTS 2019</b>	<ul style="list-style-type: none"> <li>consider use of humidification with sterile water or normal saline</li> <li>do not routinely use rhDNSase</li> </ul>	D A	3 to 1+ 1+
<b>SEPAR 2018</b>	<ul style="list-style-type: none"> <li>insufficient evidence to recommend routine use of mucolytics</li> <li>hypertonic substances recommended in expectoration &gt;10 mL per day despite other treatment</li> </ul>	strong strong	low moderate
<b>TSANZ 2015</b>	<ul style="list-style-type: none"> <li>mucoactive agents are not routinely recommended</li> <li>consider trial in frequent exacerbations</li> </ul>	weak	moderate



<b>BTA 2019</b>	<ul style="list-style-type: none"> <li>rhDNase is contraindicated</li> </ul>	strong	high
	<ul style="list-style-type: none"> <li>consider using hypertonic saline in persistent secretions despite other measures</li> </ul>	NR	NR
	<ul style="list-style-type: none"> <li>supervise first administration of hypertonic saline to assess adverse events, which can be prevented or minimized by prior administration of short-acting bronchodilator</li> </ul>	NR	NR
	<ul style="list-style-type: none"> <li>insufficient evidence to recommend routine use of mucolytics</li> </ul>	NR	NR
<b>STS 2017</b>	<ul style="list-style-type: none"> <li>DNase is contraindicated</li> </ul>		
	<ul style="list-style-type: none"> <li>nebulised saline or mannitol may increase ease of sputum expectoration and decrease its viscosity</li> </ul>	NR	B
	<ul style="list-style-type: none"> <li>be aware of airway hyper-responsiveness, as it occurs in approximately 12% of patients</li> </ul>	NR	D
	<ul style="list-style-type: none"> <li>rhDNase is not recommended as potentially harmful</li> </ul>	NR	A
<b>Pulmonary rehabilitation</b>			
<b>ERS 2017</b>	<ul style="list-style-type: none"> <li>participate in PR</li> <li>tailor to patient's symptoms, physical capability and disease characteristics</li> </ul>	strong	high
<b>BTS 2019</b>	<ul style="list-style-type: none"> <li>offer PR to those functionally limited by shortness of breath (mMRC <math>\geq 1</math>)</li> <li>consider the use of inspiratory muscle training in conjunction to PR to enhance maintenance of the training effect</li> </ul>	B	1- to 1+
<b>SEPAR 2018</b>	<ul style="list-style-type: none"> <li>participate in PR</li> <li>stable patients with mMRC dyspnoea scale <math>&gt;1</math></li> </ul>	strong	moderate
<b>TSANZ 2015</b>	<ul style="list-style-type: none"> <li>participate in PR when exercise limitation</li> </ul>	strong	moderate
<b>BTA 2019</b>	<ul style="list-style-type: none"> <li>refer to regular exercise and PR program, if available</li> <li>in clinically stable patients with chronic hypercapnic respiratory failure, non-invasive mechanical ventilation by BiPAP should be used as an adjuvant to cardiopulmonary rehabilitation</li> </ul>	NR	NR
<b>STS 2017</b>	<ul style="list-style-type: none"> <li>PR recommended as potential complementary option in moderate-to-severe disease</li> </ul>	NR	C

**Explaining BTS grade of recommendation appraisal system:** A: a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results, B: a body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+, D: evidence of level 3 or expert opinion or extrapolated evidence from studies rated as 2+.

**Explaining BTS level of evidence appraisal system:** 1+: well conducted meta-analyses, systematic reviews of RCTs, or RCTs with low risk of bias, 1-: meta-analyses, systematic reviews of RCTs or RCTs with high risk of bias, 3: non analytic studies, for example, case reports, case series.

**Explaining STS system:** A: RCTs with rich body of data or meta-analysis from RCTs, B: RCTs with a limited body of data or meta-analysis from non-RCTs, C: non-randomised trials and observational studies, D: panel consensus.

**Abbreviations:**

ERS: European Respiratory Society, BTS: British Thoracic Society, SEPAR: Spanish Thoracic Society, TSANZ: Thoracic Society of Australia and New Zealand, BTA: Brazilian Thoracic Association, STS: Saudi Thoracic Society,

RCT: randomised control trial, ACT: airway clearance techniques, o-PEP: oscillatory positive expiratory pressure, BiPAP: bilevel positive airway pressure.

NR: none reported.

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